

### **Remarks**

Applicants appreciate the courtesies extended by Examiners Borgeest and Kemmerer to Allan Fanucci and Teresa Chen during a telephone interview on October 23, 2006. The comments appearing herein are substantially the same as those presented and discussed during the interview.

Claims 31 and 36-42, as amended, appear in this application for the Examiner's review and consideration. Claims 31 and 40 have been amended to further define the present invention and in the manner as suggested by the Examiner. Claims 32-35, 43-44, 46-49, 68-71 and 83-86 are cancelled. Paragraph [0116] of the published application has been amended to correct typographical errors. In particular, SEQ ID NO. 9 was recited instead of SEQ ID NO. 10 and SEQ ID NO. 3 was recited instead of SEQ ID NO. 1. Supports for these changes are found in Fig. 3 and Table 2 of the published application. Process claims 45, 50-59, 67, 72-82 and 87-96 are currently withdrawn but it is understood that they will be rejoined when the product claim 31 is allowed. As no new matter is introduced, entry of the amendments at this time is warranted.

The Examiner maintained the rejections of claims 31 and 36-42 under 35 U.S.C. §112, first paragraph, for scope of enablement. In response, Applicants have amended claim 31 to more clearly define what variants are encompassed. Therefore, claim 31 and its direct or indirect dependent claims 36-42 are now fully enabled.

Claim 40 was also rejected under 35 U.S.C. §112, first paragraph as failing to provide enablement for a natriuretic peptide-carrier protein fusion protein wherein the carrier protein is a "bone growth plate specific protein" and for failing to comply with the written description requirement. In response, claim 40 has been amended to replace "a bone growth plate specific protein" with "selected from the group consisting of growth hormone (GH), insulin like growth factor-1 (IGF-1) and thyroid hormone (TH)", which is fully supported by disclosures in paragraph [0122] of the published application.

Based on the foregoing, all rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

The rejection of claim 31 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,434,133 to Tanaka et al. ("Tanaka") was maintained. Tanaka discloses synthesis of derivatives of CNP and a vascular smooth muscle cell growth suppressing agent that contains such peptides as an effective ingredient. In particular, position H of the Tanaka peptide formula

is Met or Gln. In contrast, in the currently amended claim 31, the corresponding position Xee is Ala, Trp, His, Lys, Ser or Gly. Thus, claim 31, as amended, is not anticipated by Tanaka and the rejection should be withdrawn.

The rejection of claim 31 under 35 U.S.C. §102(b) as being anticipated by a publication by Suzuki et al. (FEBS 282:321-25 (1991)) ("Suzuki") was maintained. Suzuki relates to a high molecular weight variant of CNP isolated from cardiac atria and ventricles of European dogfish, having the peptide sequence CFGVKLDRIGAMSGLG. In the Suzuki sequence, position Xaa is Leu and position Xdd is Ala. Applicants have amended claim 31 to include a proviso that when Xdd is Ala, Xaa is Leu, as set forth in SEQ ID NO. 54, which is different from the Suzuki sequence. Thus, none of the variants recited in claim 31 share the same sequence with the Suzuki peptide. Therefore, Suzuki does not teach the present invention and the anticipation rejection based on Suzuki should be withdrawn.

The rejection of claims 31 and 36-38 under 35 USC §102(b) as being anticipated by a publication by Ohbayashi et al. (*Clin. Exp. Pharma. Physiol.*, vol. 25, 986-91, 1998, referred to hereafter as "Ohbayashi") was maintained. Ohbayashi discloses co-administration of thiorphan with administration of CNP. Since Ohbayashi does not teach any of the CNP peptide variants of the present invention, it cannot anticipate claims 31 and 36-38 and the rejection over Ohbayashi should be withdrawn.

The rejection of claim 31 under 35 USC §102(b) as being anticipated by European Patent No. EP 0528686 to Yabuta et al. (referred to hereafter as "Yabuta") was maintained. Yabuta is directed to a process for producing a target peptide by culturing host cells transformed with an expression vector for a fusion protein of the target peptide and a protective peptide, which is a fragment of *E. coli*  $\beta$ -galactosidase. One of the examples of target peptides listed in Yabuta is CNP-22 which contained sequences identical to SEQ ID NO. 2. Since SEQ ID NO. 2 has been excluded in the currently amended claim 31 and Yabuta does not teach any of the other CNP variants recited in claim 31, Yabuta does not anticipate claim 31. Thus, the rejection of claim 31 over Yabuta should be withdrawn.

Accordingly, all rejections under 35 U.S.C. § 102(b) should be withdrawn.

Claims 31 and 40-42 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yabuta, and further in view of publications by Rivera et al. (*Science* 287:826-30 (2000)) ("Rivera") and Mericq et al. (*J. Clin. Endocrinol. Metab.* 85:569-73 (2000)) ("Mericq").

Applicants respectfully point out that the Examiner's comments were in error. First, with regard to the natriuretic peptide-carrier fusion protein in the present invention, it is well known in the art that a fusion protein remains intact unless cleavage events are specified. Thus, a skilled artisan will consider it superfluous to recite "a fusion protein not meant to be cleaved". Therefore, it is clear to any artisan that the fusion proteins, as recited in the claims, are intact. Second, as explained above, Yabuta does not teach any of the CNP variants recited in the currently amended claim 31. Neither Rivera nor Mericq remedies this deficiency. Rivera discloses a novel method of controlled release of peptides such as Growth Hormone (GH) and pro-insulin by taking advantage of a conditional aggregation domain. Mericq relates to effects of growth hormone (GH) therapies in the treatment of adolescents with GH deficiency, where administration of GH with LHRH-A is compared with administration of GH alone. There was no teaching or suggestion in either Rivera or Mericq to modify CNP-22, which is disclosed in Yabuta, to achieve the CNP variants recited in claim 31 and its dependent claims 40-42. Therefore, none of the cited references, alone or in combination, discloses CNP peptide variants as recited in the currently amended claim 31 or natriuretic peptide-carrier protein fusion protein thereof as recited in claims 40-42. Thus, the rejection of claims 31 and 40-42 under 35 U.S.C. § 103(a) should be withdrawn.

In view of the above, the entire application is believed to be in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues in order to expedite the eventual allowance of the claims.

Respectfully submitted,

Date 11 / 9 / 06 for: [Signature] (Reg. No. 57,073)  
Allan A. Fanucci (Reg. No. 30,256)

**WINSTON & STRAWN LLP**

Customer No. 28765

212-294-3311